DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, Claims 1-8 and 17-18, in the reply filed on 11/12/2007 is acknowledged. Applicant's election without traverse of the following is also acknowledged: The low-molecular weight, water soluble and non-peptide drug has (1) a phosphate group, (2) a carboxyl group, and (3) is a prostanoid.

Claims 1-8, 17-18 are pending and currently under consideration.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 17-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The phrase "An anti-inflammatory/anti-rheumatoid drug containing nanoparticles encapsulating a water-soluble steroid according to claim 1, as an active ingredient" in Claim 17 is vague and indefinite. Claim 17 recites the limitation "as an active ingredient" in Claim 1. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –

> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 3-4 are rejected under 35 U.S.C. 102(b) as being anticipated by Allemann et al (Alleman et al, PEG-coated poly(lactic acid) nanoparticles for the delivery of hexadecafluoro zinc phthalocyanine to EMT-6 mouse mammary tumors, the Journal of Pharmacy and Pharmacology, 1995, 47(5), 382-387; Document provided by Applicant). Allemann et al discloses nanoparticles comprising hexadecafluoro zinc phthalocyanine (a low-molecular weight, water-soluble and non-peptide drug made hydrophobic by metal ion) encapsulated in poly(lactic acid) and polyethylene glycol (a surfactant) (see abstract; Figure 1). Hexadecafluoro phthalocyanine has a molecular weight of 800 g/mol.

As explained above, the phrase "characterized in that a low-molecular weight, water-soluble and non-peptide drug is made hydrophobic by metal ion" in Instant Claim 1 is vague and indefinite. The Examiner finds one reasonable interpretation of this phrase to encompass adding zinc to a said drug, forming a new hydrophobic drug.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-8, 17-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Horisawa et al (Horisawa, Prolonged Anti-Inflammatory Action of DL-Lactide-Glycolide Copolymer Nanospheres Containing Betamethasone Sodium Phosphate for an Intra-Articular Delivery System in Antigen-Induced Arthritic Rabbit, Pharmaceutical Research, 2002, 19(4), 403-410) in view of Stahl et al (Stahl et al, Handbook of Pharmaceutical Salts: Properties, Selection, and Use, 2002, Publisher: Wiley-Vch, Weinheim), in further view of US 2938916.

Horisawa et al discloses DL-lactide/glycolide copolymer nanospheres incorporating betamethasone sodium phosphate (see p 403, col 1, first paragraph to col 2, first paragraph). The disclosed nanospheres further comprise polyvinylalchohol (PVA) (see p 403, Preparation of BSP-Loaded Nanospheres). The disclosed nanospheres have a mean diameter ranging from 302 ± 43 to 482 ± 89 nm. Horisawa discloses that direct injection of colloidal steroid-crystals into the joints is effective for RA disease. The drug rapidly disappeared, however, from the articular cavity (see p 403, col 2, first full paragraph). Horisawa further discloses that DL-lactide/glycolide copolymer containing nanoparticles are desirable because it is biodegradable, and suitable for drug delivery to inflamed synovial tissue due to their ability to penetrate into the synovium (see p 403, introduction). Direct intra-articular injection of the disclosed nanosphere system provided a prolonged pharmacological efficacy in the joints of arthritic rabbits (see p 409, conclusion). In addition, the disclosed nanosphere system was safe and provided prolonged local- anti-inflammatory action in joint diseases without biologic damage.

Horisawa et al fails to disclose nanoparticles characterized in that a low-molecular weight, water-soluble and non-peptide drug is made hydrophobic by metal ion and is encapsulated in nanoparticles formed with poly(lactic-co-glycolic acid) or poly(lactic acid), and a surfactant is applied to the surface of the nanoparticles of poly(lactic-co-glycolic acid) or poly(lactic acid).

Stahl et al discloses that making a drug molecule more water-soluble can be a drawback (see p 2, last paragraph to p 3, first paragraph). There is a general tendency

that the more water-soluble a compound is, the more diffusible it is. This causes it to be less specific in its activity, more liable to rapid elimination, and therefore shorter acting. Sparingly soluble salts of small molecule drugs have been prepared to retard drug release (see p 103, Section 4.3.7). Examples include imipramine pamoate vs. imipramine hydrochloride, diclofenac resinate vs. diclofenac potassium, propranolol laurate vs. propranolol hydrochloride. In the last example, the laurate salt of propanolol not only produced an expected retardation of activity but simultaneously improved bioavailability when compared with the hydrochloride.

'916 discloses water-insoluble zinc salts of steroid phosphate esters, having cortisone-like, anti-inflammatory activity and processes for preparing the same (see col 1, first paragraph). Among the compounds which may be prepared according to the patent invention are 9alpha-fluorohydrocortisone-21-phosphate zinc salts (see col 1-2, bridging paragraph).

One of ordinary skill in the art would be motivated to combine the disclosures of Horisawa et al, Stahl et al, and '916 and prepare the nanoparticles of the instant invention, with a reasonable expectation of success. In the effort to produce nanoparticle formulations of betamethasone phosphate with improved release profiles, one would reasonably prepare a nanoparticle comprising the zinc salt of betamethasone phosphate encapsulated by DL-lactide/glycolide copolymer and a surfactant, such as poly(vinyl alchohol). The sparingly soluble betamethasone phosphate zinc salt should retard the drug release relative to soluble betamethasone phosphate, hindering the rapid disappearance of the drug from the articular cavity, and improving

pharmacological efficacy in the subject. One of ordinary skill in the art could readily make the zinc salt, as disclosed by '916. Encapsulation of the salt in DL-lactide/glycolide and poly(vinyl alchohol) is desirable owing to its precedent in providing a safe, prolonged pharmacological efficacy in the joints of arthritic rabbits without biologic damage. One of ordinary skill in the art would reasonably choose a particle diameter ranging from 302 ± 43 to 482 ± 89 nm, as this was the optimum value for the nanoparticle system disclosed by Horisawa et al.

As explained above, the phrase "characterized in that a low-molecular weight, water-soluble and non-peptide drug is made hydrophobic by metal ion" in Instant Claim 1 is vague and indefinite. The Examiner finds one reasonable interpretation of this phrase to encompass adding zinc to said drug to form a hydrophobic salt.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to PAUL DICKINSON whose telephone number is (571)270-3499. The examiner can normally be reached on Mon-Thurs 8:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin H. Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Paul W. Dickinson
Examiner
AU 4173

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/Ardin Marschel/
Supervisory Patent Examiner, Art Unit 1614